INSIDE SCIENCE TRAIN2GAIN WHAT'S ON CNIC & SOCIETY

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More on the CNIC at www.cnic.es Please send any comments or suggestions to flois@cnic.es I have received many positive comments about the first issue of CNIC Pulse, which is a testament to the general interest in what we do in this center. Of course, if you're going to recount something you first have to have something to say. But that's no problem at the CNIC. One of the things I like most about this center is the unceasing activity here. There is no dead time and no talent is wasted, something that was evident in the first issue of **CNIC Pulse** and which is demonstrated again here.



Dr. Valentín Fuster, CNIC Director

WE TALK ABOUT WHAT WE DO BECAUSE WE HAVE A LOT TO SAY

In the section more strictly dedicated to pure science, we present a publication that combines scientific efficiency and ingenuity in the description of a new method that allows researchers to visualize the formation of atherosclerotic plaques in mice. The method uses a gadget made with what at first glance seems a commonplace material, modeling clay; but the results have amazed the scientific community.

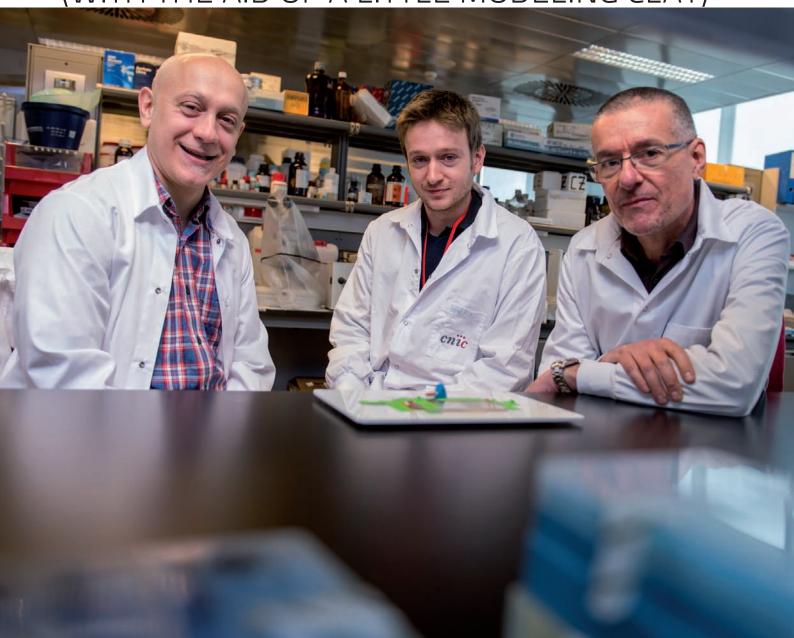
The scientific community has without doubt also been impressed by the past, present and future career path of one of our young research leaders Nadia Mercader, to whom the European Commission has granted one of its prestigious and generously financed ERC awards to fund her search for the keys to cardiac regeneration, as explained in another of the articles.

We have also found space in our pages for the Polypill, a veteran CNIC project now very close to becoming available in Spanish pharmacies. And this winter issue is completed by a pair of articles on the CNIC-Joven Training Plan. One tells the experience of a young CNIC scientist who has passed through several of our training programs. And the other presents RES@CNIC, one of the latest additions to join the CNIC-Joven family, aimed at resident physicians.

This issue also includes an updated scientific calendar and details of events related to corporate responsibility- the Pro CNIC Foundation is a fundamental pillar of our center and we are always delighted to highlight it. I hope you enjoy this issue of CNIC Pulse as much as the first and that you will continue to enjoy future issues. I have no doubt that we will never be at a loss for things to say.



LIVE 3D IMAGING OF ATEROSIS (WITH THE AID OF A LITTLE MODELING CLAY)



They say that you should know your enemy, and this is precisely what Andrés Hidalgo, Vicente Andrés and their team set out to do, with the help of science, a microscope, and a healthy dose of imagination. The CNIC researchers have scored a first in the cardiovascular field, recording images of the formation of an atherosclerotic plaque in a living animal at high resolution and in specific locations—the large arteries in which the disease normally develops, a feat never achieved before. Their work is reported in *Circulation Research*, one of the leading journals in the cardiovascular area. The first author of the study is Raphael Chèvre, another young investigator at the center.

There is little new that can be said about the importance of atherosclerosis. Through its major consequences—heart attack (myocardial infarction) and stroke (cerebral

ischemia)—atherosclerosis is the main cause of death and disability in developed countries. But while we know a great deal about its impact on health and socio-economic wellbeing, there is still a lot to learn about how atherosclerosis develops and why it has different effects in different people.

We do know that atherosclerosis is a chronic inflammatory process characterized by the incorporation into the arterial wall of cells of the immune system (monocytes, lymphocytes and neutrophils) and blood platelets, which participate very actively in all phases of the disease. But which cells arrive first? Are there changes at different phases of the disease? Is the process the same in people with diabetes and hypertension (to mention just two known risk factors)? Similar processes

have been studied in detail in living animals before, but only in atherosclerosis-free narrow vessels and not where it really matters, in the large arteries where the disease develops.

High resolution live imaging of atherosclerotic plaques forming in large arteries has been impossible until now for a very simple reason: these arteries move with the motions of breathing and heartbeat.

Through its major consequences atherosclerosis is the main cause of death and disability in developed countries

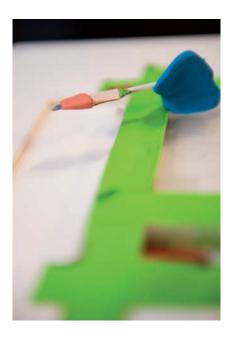
So what was needed was a way to stabilize one of the vessels prone to developing atheroma plaques. And this is where a little ingenuity came into play. The team devised a simple apparatus comprising a metal board and a material not usually associated with cardiovascular research, modeling clay. With this, they were able to stabilize the carotid artery without affecting the blood flow, enabling them to use imaging technology based on high-speed multichannel epifluorescence and an array of flourescent probes.

The study was conducted with mouse strains susceptible to developing atherosclerosis, and with this method the team was able literally to shine a light on key processes of plaque formation at different phases and at high temporal (sub-second) and spatial (sub-micron) resolution, in a manner never achieved before.

Using several fluorescence channels, the scientists studied different populations of blood cells (leukocytes and platelets) simultaneously in real time, tracking their interaction with the cells lining the blood vessel wall. Through partnership with Oliver Soehnlein and Christian Weber at the universities of Munich and

Amsterdam, the authors demonstrated that the method is compatible with multiphoton microscopy, a technique that can be used to produce three-dimensional images of leukocytes moving over the arterial wall affected by atherosclerosis.

It's still too early to say what we will learn with this method. But it is sure to generate a lot of information, and the team have already made important discoveries. For example, they were able to confirm that the incorporation of blood cells into the damaged arterial wall occurs at a very early stage of atherosclerosis. And they also detected differences in the rates at which different inflammatory leukocyte populations are recruited, detecting which cells accumulate first and how the pattern changes as the disease progresses. There is still a long way to go, but we can now see the way ahead.





Nadia Mercader never imagined she would end up working with zebrafish, but it is her research into this species that has now won her one of the most important awards from the European Commission, a European Research Council (ERC) starting grant. One thing this biologist has always known, however, is that to succeed in science you need to be adaptable, and that includes being ready to switch research model if necessary. During her postgraduate training at the CSIC, Nadia worked with several models. As her training progressed, the now Dr. Mercader settled her interests on development and regeneration, and eventually began to work with zebrafish. Key advantages of this relatively recent addition to the biologists' toolkit include the optical transparency and rapid development of its embryos- which allow embryonic development to be observed in real time- and the extraordinary capacity of adult animals to regenerate damaged tissue. The zebrafish genome is moreover remarkably similar to our own.

Despite these advantages, Nadia recognizes that "there's no such thing as the perfect model; you just have to find the best tools and models to address the biological question you want to ask." The changes in the experimental models she has employed over the years have in fact tracked the changes in the questions that have interested her. And it is precisely this flexibility, together with the creativity that she has demonstrated throughout her career, that seem to have impressed the expert ERC panelists who awarded her €1.5 million in a grant that started in 2014.

When Dr. Mercader joined the CNIC she shifted her focus from the regeneration of limbs to regeneration of a more vital organ, the heart. Although she maintains her general interest in "how regeneration uses embryonic mechanisms," her work now centers more on "how, in response to injury, the organism has to decide between rapid repair with the formation of a scar or the more gradual process of regenerating functional tissue."

This is of course something that unfortunately does not happen in humans. If it did, cardiovascular diseases like infarction would not be so life threatening, since the heart, though it would be damaged, would take charge of regenerating itself. This is exactly what happens in zebrafish, even in adults, and achieving this one day in humans is the holy grail of cardiac regeneration research.

Nadia believes that one of her published papers was particularly important in clinching the ERC support. It was an especially memorable article because it was her first as a group leader at the CNIC. "I did it with my first PhD student, Juan Manuel González Rosa. Although the capacity of the zebrafish heart to regenerate was already known [since 2002], this had only been demonstrated after surgical removal of tissue (resection), and we were unsure if it could regenerate equally well after damage based on wounding rather than on amputation." The analysis showed that it indeed can, and further that this was not a question of a choice between scarring and regeneration. "It isn't the case that the zebrafish heart can't regenerate if it forms a scar; rather, despite forming a scar it is still able to regenerate." This study, published in the journal

Development, generated a great deal of interest and many investigators visited the CNIC to learn the technique for causing localized damage to the heart (it involves applying a cold needle) and how the small heart regenerates afterwards.

Securing the grant was not easy. Although Dr. Mercader applied as an individual investigator, she well knows the debt of gratitude she owes to all those who helped her, including staff in the CNIC project office and her researcher colleagues who encouraged her to apply. The whole process took about a year. "You think that it is going to be so difficult, so competitive, that there are sure to be extraordinary candidates; so what chance is there that they will give an award to me? Only 10% of applications succeed." But in the end all the effort and nerves were rewarded in August 2013, when she received an email from the ERC.

Far from being like winning the lottery, the award has kept Nadia working as hard or harder than ever. Above all, the new funding is allowing Nadia to contract new staff. She wants to build a team of about eight, which of course brings with it the cost of research materials and the articles she hopes to publish.

Asked about her plans, Nadia Mercader has a clear vision of what she hopes to achieve in the five years of the ERC-funded project: "I want to contribute to improved understanding of the mechanisms by which the zebrafish heart takes the decision to remove the scar and regenerate lost tissue; what are the cellular and molecular mechanisms, what types of cells and what genes are involved." The idea is that the knowledge acquired in zebrafish will one day have a wider application, perhaps leading to successful regeneration of damaged heart tissue in humans.



It's an all too familiar story. A man around 50 years old has a heart attack. Thanks to medical advances the treatment he receives is effective, and he is soon out of immediate danger. A little while later he is out of hospital. But even after his return home nothing will ever get back to normal: his risk of suffering another cardiovascular event is six times the average for a healthy individual of his age.

Cardiovascular disease is the primary cause of death worldwide. The two most common clinical manifestations of the disease are heart attack—or myocardial infarction—and stroke. Over the past decades, physicians and other scientists have made major advances in the diagnosis, treatment and prevention of cardiovascular disease. Today we know that the key to reducing the probability of suffering this disease lies in the control of risk factorsincluding smoking, high blood pressure, diabetes, high blood cholesterol and lack of exercise.

POLY PREVENTION

TO STOP REPEAT HEART ATTACKS AND STROKES But what happens when you have already had a heart attack or stroke? Clinical studies leave us in no doubt that even after a cardiovascular event, prognosis is improved by the adoption of healthy lifestyle habits, such as stopping smoking, taking exercise, and eating a healthy diet. But this is not enough. The patient also needs to take preventative medication, known as secondary prevention, for the rest of his life.

The medicines that improve life expectancy after a heart attack are well known. All heart attack survivors with no contraindications should take a statin to reduce cholesterol, an ACE inhibitor to lower blood pressure, a betablocker, and aspirin. The bad news is that this medication needs to be taken every day, requiring patients to take a large number of pills.

Even though patients in this situation are acutely aware of the importance of their medication regimen, sticking to it is not easy. Around half of all patients with a chronic illness do not take their medicines as prescribed. Sometimes they forget to take them, or alter the treatment schedule. And sometimes patients simply stop taking their medicine altogether. This phenomenon, known as non-adherence to treatment, weakens protection against repeat events and increases complications. Treatment adherence is influenced by many factors, but one of the most important is the complexity of the prescribed medication regimen. The more pills a patient has to take and the more complex the treatment schedule, the higher the chance that he or she will not adhere to treatment

WHEN PRESCRIBED APPROPRIATELY, HE POLYPILL WILL BE THE IDEAL COMPLEMENT TO THE ADOPTION OF THE HEALTHY LIFESTYLE

Added to this problem is the question of cost. The drugs presribed for secondary prevention can be expensive, especially in lowand middle-income countries, and this can effectively exclude most of the population from receiving appropriate treatment. As a consequence, the global epidemic of cardiovascular disease continues to grow.

Several years ago, researchers came up with the idea of combining three or more drugs in a single capsule, a polypill. By reducing the number of pills patients need to take every day, the idea was that treatment would be simplified, adherence increased and costs reduced. But combining drugs in a single preparation is technically challenging and requires a major investment of time and money, and many physicians and pharmaceutical industry leaders were skeptical. It seemed that the dream of a polypill would not become a reality.

In 2006, CNIC general director Dr. Valentín Fuster, having himself witnessed the inadequacy of cardiovascular prevention in some developing countries because of the high cost and scarcity of medication, considered that the time was ripe for the development of a polypill. This would not only simplify treatment, but also make it cheaper and therefore affordable in low- and middle-income countries.

To carry this project forward, it was necessary to find a pharmaceutical company prepared to take on the challenge of investing in a project that was both scientific and social in its focus. Finding one was not easy. The polypill concept is not a typical drugs company money spinner; the company that took on this project would need to be motivated as much by corporate social responsibility as anything else.

Ferrer Laboratories accepted the challenge and in September 2006 began working on the project with a passion. There followed many meetings, consultations with national and international agencies, and countless hours of laboratory research and clinical trials. The final result was two distinct polypills. One of them is today the only polypill to be commercialized in Guatemala, Mexico, the Dominican Republic and Argentina. The other has been offered for assessment to the health authorities of several European countries.

At the same time, the CNIC, with Dr. Fuster as lead investigator, is carrying out a major clinical trial called FOCUS. When completed in June of this year, its results will contribute to an improved knowledge of cardiovascular prevention and the role of the polypill, and will very likely win wide acceptance for this therapeutic strategy that eases the life of heart attack and stroke survivors by simplifying their medication. When prescribed appropriately, the polypill will be the ideal complement to the adoption of the healthy lifestyle that all patients should adopt: not smoking, eating a healthy diet and taking exercise. This is, without a doubt, the simplest poly prevention.

In Circulation: Cardiovascular Genetics

PREDICTING RISK

Restenosis is the main complication experienced by patients after being fitted with a drug eluting stent, a device that saves lives every day. Now, researchers in the Cardiovascular Research Network (Red de Investigación Cardiovascular, RIC), in a projec led by Vicente Andrés, have identified new biomarkers that predict when this is likely occur, signaling a great advance for patients.

Excellence

SUCCESS IN THE 7™FRAMEWORK PROGRAMME

We've done it again. Success is the best word to describe the CNIC's path through the European Commission's Seventh Framework Programme (2007-2013; FP7), in which we are the third-ranking Spanish center in funds awarded under the PEOPLE Programme. Some of the Center's key FP7-funded projects are

- An ERC Advanced grant for the study of novel modes of immunomodulation
- Four ERC Starting grants, for projects related to necrosis, obesity, mature B cells and cardiac regeneration
- The CNIC-coordinated CARE-MI consortium, for the study of ischemic
- The ambitious FOCUS study into the
- Two Initial Training Networks: CardioNet and CardioNext



In Nature Communications

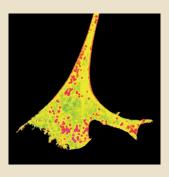
KEYS TO A VITAL JOURNEY

A team of CNIC researchers directed by Francisco Sánchez-Madrid (María Mittelbrunn and Carolina Villarroya-Beltri), has described for the first time the mechanism through which microRNAs—small RNA molecules that regulate the expression of specific genes—are encapsulated in nanovesicles that 'journey' between cells, a finding that is sure to stimulate discussion

In EMBO Molecular Medicine

SCORING A STRIKE AGAINST ATHEROSCLEROSIS

Working hand in hand, researchers at the CSIC (Miguel Campanero) and the CNIC (Juan Miguel Redondo and Nerea Méndez) have paved the way to a future strike against atherosclerosis. The discovery: inhibition of a single protein could improve the treatment of this disease, which would certainly be welcome. As is the norm with basic research, we will have to wait, but contacts have already been established with the pharmaceutical industry.





CALL CLOSES MARCH 7 La Caixa-Severo Ochoa International PhD

The La Caixa Foundation continues its support for the CNIC International PhD Program. In 2014 the La Caixa Foundation will provide funding for four recently qualified graduates.

Eligibility requirements:

- A university degree in Biomedical Science or a related discipline awarded within the European Higher Education Area. The degree should qualify for enrollment on a PhD program in the student's home country.
- Completion of studies no more than two years before the closing date for applications.
- A solid working knowledge of English.
- No research-related relationship with the CNIC for more than six consecutive months before the closing date for applications.



CALL CLOSES MARCH 20 **CICERONE Program**

This program gives university students first-hand knowledge of biomedical research to help them make informed choices about the possibility of pursuing a scientific career in the future.

The CICERONE Program is open to advanced undergraduate students studying towards a biomedicinerelated university degree. Participants extend their scientific training through hands-on experience of laboratorybased biomedical research during the summer recess. In addition to carrying out a supervised research project, the students also attend CNIC seminars.



CALL CLOSES APRIL 2014 **CNIC International Incoming** Fellowships: CNIC IIF

The CNIC has launched the fourth call of the CNIC International Incoming Fellowships program for young group leaders. The program is supported by €2.4 million from the European Commissison through the COFUND Programme, within the Marie Curie Actions theme in FP7.

This program aims to increase the mobility within Europe of experienced researchers in the cardiovascular research area. The program has been designed to support transnational mobility of researchers and to broaden and deepen their individual competencies, particularly in terms of acquisition of complementary skills needed to attain or strengthen a senior independent position in biomedical research.

The program offers fellowships for experienced researchers at two career stages, depending on experience and profile: 1) Starting Fellowships (SF), and 2) Advanced Fellowships (AF). The researchers will have a 3-year contract with additional funding for travel and research-related costs. They will also receive a benefits package that includes full social security cover, a flexible salary package, life insurance for death or permanent disability, civil liability insurance, a work and family life balance, assistance with nursery care, and language training (English and Spanish).



CALL CLOSES APRIL 2014 **CNIC International Postdoctoral** Program: CNIC IPP

In February the CNIC launched the second call of its International Postdoctoral Program, supported by €1.6 million from the European Commission through the COFUND Programme, within the Marie Curie Actions theme in FP7.

The CNIC IPP supports transnational mobility of postdoctoral researchers with the aim of broadening and deepening their individual competences, particularly in terms of acquisition of complementary skills needed to become an independent group leader in the future. The program is open to researchers who hold a PhD degree at the time of the application deadline.

The present call is the second of a total of five annual calls, each offering six positions. Successful applicants are hired on 3-year contracts. Researchers on the CNIC IPP program receive additional funding for travel and a benefits package that includes full social security cover, a flexible salary package, life insurance for death or permanent disability, civil liability insurance, a work and family life balance, assistance with nursery care, and language training (English and Spanish).



CALL OPENS APRIL 2014 **INVESMIR Program**

The INVESMIR program offers medical professionals, during their specialization period as resident interns, the opportunity to further their training through a research project in one of the CNIC's laboratories, under the supervision of a CNIC scientist. An important goal of the program is for

participants to establish contacts and collaborations in the CNIC that will support them, after completion of their MIR specialization training, in pursuing their own research projects at their centers within the Spanish National Health System.

The duration of the stay is flexible (between four and six months), so as to conform with the regulations for resident intern training in the participant's home center.



CALL OPENS APRIL 2014 ACÉRCATE Program

The ACÉRCATE Program offers senior high school students studying natural and health sciences the chance to experience life as a biomedical researcher, with the aim of awakening interest in a career in research. Participants spend two weeks at the CNIC learning modern techniques used in biomedical research, conducting supervised experiments, operating sophisticated scientific equipment and presenting the results of their work, all under the supervision of our researchers.

The ACÉRCATE Program will run for two consecutive weeks in July.



CALL OPENS MAY 2014 **MASTER Program**

This grants program provides individual funding for 12 months' study towards a Master's degree at a Spanish university. The program is directed at students who are going to study for a PhD in one of the CNIC's labs; completion of an official Masters (Máster Oficial) has been introduced as an obligatory stage towards a PhD in Spain, in accordance with the Bologna process to standardize academic qualifications across Europe. Candidates, who can be of any nationality, must be university graduates in a discipline related to biomedicine and have a grade average sufficient for acceptance on a Máster Oficial program at a Spanish University. The experimental component, if there is one, must be carried out in a CNIC laboratory.

Eligibility requirements:

- Applicants must not be in receipt of any other grant or financial assistance from public or private bodies (Spanish or foreign).
- Students must have a formal offer from one of the CNIC's laboratories to carry out the experimental component of their Masters course and their future doctoral thesis.
- Applicants must have an grade average of 2.0 or above for their completed credits (scale 1 to 4)

Full details of all CNIC training programs and fellowships can be www.cnic.es/en/formacion/index.php. Aurora Bernal exudes enthusiasm as she talks. This is as evident when she speaks about her career as when conversation moves to the CNIC, the center where she has been training since 2010, and where she has experienced one of its standout projects—the CNIC-JOVEN training program—"from both sides." This young researcher is in no doubt that the CNIC's commitment to training produces tangible outcomes. So much so that she would be happy to end up working here in the long term.

PASSIONATE ABOUT TRAINING AURORA BERNAL



Aurora was "completely sure" early on that she wanted to study biology. As often happens, it was "a brilliant teacher" who set her on her career path, when she was in her final years at high school. "That's how it all started", and Aurora subsequently went on to study Biology at the *Universidad Autónoma de Madrid*. It was during her undergraduate studies that Aurora first came into contact with the CNIC, though at that time she had no inkling of the important role the center would come to play in her life. "In the spring the UAM Careers Fair was held and that was where I met the CNIC's head of training. Funnily, it was almost a chance meeting; some friends from another department happened to see the CNIC stand and stopped to ask for information, thinking of me," she recalls.

It was at the stand that Aurora first heard about the CICERONE program, which gives students in their final years (she was already in her fifth year, and on the point of graduating) first hand experience of research at the CNIC during the summer. "At the time I was studying evolutionary genetics, which in principle bore no relation to the CNIC; it wasn't even biomedicine. But the techniques were similar." And a year before this Aurora had gained experience of health research, at the Fundación para la Investigación Biomédica at the Getafe University Hospital near Madrid, where she worked with a research team attached to the intensive care unit. "I saw all facets of research in a model of lung injury that the group worked with; this was my

introduction to biomedicine."

When she arrived home from the careers fair,
Aurora visited the CNIC web site and drew up her own
career route map. "I noticed that in addition to the CICERONE
program there were also Masters grants, and I said to myself,
'It would be great to find a group I could work with over the
summer, then continue with the same group for my Masters,
and if all goes well, do my PhD with the same group as well'."
She carefully studied the available group leaders' profiles; "It's
very important to me that whatever I do has to something I'm
passionate about." The 'spark' came with Beatriz González,
whose group investigates cardiovascular related risks of
obesity. Both agreed that if they worked well together over the
summer, an application for a Masters grant would be on the
cards.

"It would be great if I were to end up back at the CNIC, at the end of the day it's my scientific home."

"You always learn, whether you're a trainee or the trainer."

Aurora graduated in June 2010, applied to the CICERONE program and was awarded a place. Although she received no funding during those two months, the training and guidance were in many ways more valuable than money. And above all, the experience confirmed that Aurora and her boss gelled perfectly. So the next step fell into place and Aurora applied for a Masters grant to study molecular biomedicine. "I spent four months training at the UAM and came back to the lab for the practical project." This time Aurora did receive financial support, which "provided welcome encouragement" for her year-long Masters studies. Studying for her PhD in the lab where she had started her training seemed the logical way forward, and Aurora carried on at the CNIC after the end of her Masters

fellowship. In December 2012 she was awarded a Severo Ochoa professional training award to finance her predoctoral training, which is scheduled to conclude in December 2016.

"It's hard to believe looking back, but everything's worked out exactly as I hoped", comments Aurora. Her PhD project investigates the migration of stem cells and how this can be promoted to ensure that greater numbers arrive at the target organ. "The aim is to use these stem cells in regenerative therapy after tissue damage."

Apart from being a direct beneficiary of the CNIC-Joven Program, Aurora is an enthusiastic contributor from "the other side of the lectern", having taught participants in the ACÉRCATE program, other CICERONE students who have followed in her footsteps, and also technicians training at the center. "You always learn, whether you're a trainee or the trainer."

The young investigator has no doubt that the CNIC's investment in training brings benefits to the center. She herself, for example, has published several articles and a review, and she emphasizes that "This is tangible productivity for the CNIC." Although she has no complaints, she finds it regrettable that people might be unaware that the opportunities she has enjoyed are available. This motivated her last year to attend the AULA International Student Fair in Madrid, to stand as a living example of all that the CNIC's training programs have to offer. And she also takes every opportunity to recommend the center to friends and acquaintences.

Aurora knows that when she completes her thesis she will have to spend "a long period" working outside Spain. This is a challenge that she relishes, and an important part of her motivation is the opportunities this experience will give her on her eventual return to Spain. "It would be great if I were to end up back at the CNIC," she concludes, "at the end of the day it's my scientific home."

PHYSICIANS AND RESEARCH



A PRODUCTIVE ALLIANCE

Unlike in other countries, in Spain it is quite usual for physicians never to set foot in a research laboratory after completing their compulsory practical project in the early years of medical training. Excellent doctors—the healthcare records leave no room for doubt—nonetheless don't use their accumulated expertise to make a contribution to research. This problem could be solved easily if clinicians had more contact with the world of biomedical

research. This is the inspiration behind the RES@CNIC program, created just two years ago as part of the global CNIC-JOVEN training plan. RES@CNIC is designed specifically for medics in the first years of their residency in a specialty related to cardiology or cardiovascular surgery.

Anyone who has taken the exams for the MIR (the Spanish medical residency program) and gone through the five years of training in one of these complex and fascinating specialties knows that during those years time is scarce. But it is nonetheless worth making time to learn about research or, so it would seem from the success of RES@CNIC, which enjoys enthusiastic support from researchers at the CNIC and those who combine this role with their work as physicians in Madrid's hospitals, like Borja Ibáñez and Jesús Jiménez Borreguero.

It is these CNIC scientists (eight in total) who, from January to March, are explaining the inner workings of biomedical research to the 15 RES@CNIC trainees selected for 2014. The participants will learn about the latest techniques used in the CNIC laboratories, which are among the best equipped in Spain.

RES@CNIC fellows receive no payment and have no contractural relationship with the CNIC. But this has not

Res@CNIC Program

Intended for: Medical professionals during the first years of their specialization period as resident interns.

Content: Theoretical and practical training. Participants learn about and become familiar with the latest techniques in biomedical research, always under the supervision of one of the CNIC's scientists.

Venue: The CNIC laboratories.

Duration: Maximum of 9 consecutive weeks.

Call: July.

stemmed interest, and the CNIC received many applications for this second year of the program, a clear demonstration that the general low involvement of physicians in research does not reflect any lack of interest on their part.

The young physicians selected for the program, who come from nine Spanish hospitals, will spend nine intense weeks

at the CNIC. The mornings are dedicated to a specifically designed taught module, and in the afternoons it's time to don lab coats and get down to work at the bench. This full-time course not only provides training but also helps to forge links and collaborations. The idea is that, after completing their medical residency, these professionals will continue their research programs at their respective hospitals, always in partnership with the CNIC.

The RES@CNIC schedule includes 'homework'. At the end of their spell at the CNIC, participants have to prepare a short written report describing the work carried out, and they also present their work in a talk to their colleagues and supervisors.

The reaction to the first year of RES@CNIC was very positive. In the words of one former participant, "The way they received us was exceptional; they made a real effort to involve me in the research they are carrying out." Another echoed these sentiments. "The people were great, and that really helped us to integrate."

RES@CNIC is making a real contribution to forming a productive alliance between medicine and research, one that in the long term will, without a doubt, produce benefits for patients.

This is an area that can only be described as promising. A new way of doing medicine that in a few years might revolutionize our very idea of what medicine is. Eric Bush is Director of Translational Medicine at miRagen, one of the companies that have given their support to CardioNext. This European Commission funded Initial Training Network, coordinated by the CNIC, is training 12 predoctoral students so that they not only complete a PhD thesis but also learn how to move in the world of business. Bush attended the CardioNext kick-off meeting in Madrid on February 17-18.

What can you tell us about miRagen?

We are a biopharmaceutical company located in Boulder, Colorado. Our mission is to develop RNA-based therapeutics for unmet medical needs. The primary focus of miRagen is to develop RNA therapies that target microRNAs.

Interview

Eric Bush

Director of Translational Medicine at miRagen



"WE ARE AT THE FOREFRONT OF A NEW PHARMACOLOGY"

What's special about this approach?

MicroRNAs have evolved to regulate multiple pathways in parallel. It's a very internal regulatory mechanism that's only recently been described, and what's very exciting about it is that it offers new therapeutic inroads into developing drugs that instead of targeting a single gene or a single gene product- for example a receptor or enzyme- we have the opportunity to target an entire pathological pathway with a single therapeutic agent.

What diseases are you targeting?

One area that might particularly benefit from this approach is

cardiovascular, where the disease process associated with heart failure or post MI remodeling can be multifactorial. Targeting single receptors or enzymes can help but it's been a very long time since there has been a blockbuster drug developed for heart failure. One of the reasons is that there are many processes going on at the same time, and so miRagen's most advanced programs are in this setting.

Do you have products in clinical development? At what stage are they?

We are at the forefront of a very new pharmacology. It's a very new field with a lot of promise, but as with

any new technology there's a lot to learn. We hope to be in the clinic in the next few years. Our most advanced programs are in the later stages of preclinical development and are related to heart failure. We are very fortunate to have partnered with Servier, a major European pharmaceutical company, for this program, but we also work without partners on other projects at earlier stages of development.

How did miRagen get started?

One of the keys was initial discoveries in Eric Olson's Lab, one of our scientific cofounders and a leading light in the cardiovascular field. Other discoveries made by another of our cofounders, Eva van Rooij, described a number of microRNAs involved in heart failure and post MI remodeling, and together these findings served as the scientific starting point for some of the original cardiovascular programs in miRagen's pipeline. With these discoveries we had the targets, but to make drugs you also need the chemistry. And the chemistry for targeting microRNA is different from small molecule chemistry. We're talking about making oligonucleotides—short segments of synthetic RNA that, once modified chemically, can be used for therapy. We are very fortunate that Boulder is a world-leading center of excellence in synthetic nucleoside chemistry. This is the home of Tom Cech, who won the Nobel Prize for his discoveries in RNA biology.

Research is important in all pharmaceutical companies, but I'm guessing that in yours it may be even more important than usual.

Research is a vital element of what we do. This is a very new field and we need to do a fair amount of research in order to translate our findings to the clinic. We are discovering things every day through our research team in Boulder, which comprises biologists and chemists working together to understand how to turn promising microRNAs into drugs for specific indications.

What do you expect from the young CardioNext student who will spend several months training with miRagen?

It's a little early to say because the visit is still two years ahead, and the student's work with us will to a large extent be determined by the progress made in the first part of the Cardionext project. But we foresee that the student who comes to miRagen will have the opportunity to see how drug development works inside our company and to contribute to that research based on earlier findings in the CardioNext project.



The CNIC brings the best regarded CARDIOVASCULAR DEVELOPMENT

meeting to Madrid

José Luis de la Pompa was already an experienced cardiovascular researcher when he attended his first *Weinstein Cardiovascular Conference*, in 2005. "I was starting to tire of the Keystone meetings [the other 'big meeting' in the cardiovascular development field] because most of the presentations stuck to the published data", he recalls. José Luis is the driving force behind bringing the Weinstein conference, probably one of the most important

in the world, to Madrid in 2014. José Luis is quick to emphasize all the help he received from his scientific colleagues and the CNIC management, and recognizes that presenting the proposal and organizing the meeting has required a great deal of hard work and time. But all the effort will be rewarded come May 8, when the *llustre Colegio Oficial de Médicos de Madrid* hosts between 300 and 350 researchers from all over the world, who will enjoy a full program with "an innovative twist" on the classical Weinstein format.

The coordinator of the CNIC's Cardiovascular Developmental Biology program knows the history of these meetings in minute detail. The story began at the end of the 1980s, when the Weinsteins—a couple who worked as project evaluators at the US National Institutes of Health (NIH)—realized that there was no conference program in their country that dealt with heart development. Jose Luis explains that "At the time there was an emerging recognition that many congenital heart conditions have a clear genetic basis and that by understanding the mechanisms of heart development using a range of systems we could gain an understanding of human disease." The Weinsteins devised a program of periodic meetings, and support from the prestigious investigator Roger Markwald ensured that they would be held annually. An enthused José Luis explains that "What makes these meetings different is that most of the speakers are students or post-docs and the data they present are not yet published; there are also keynote lectures by leading researchers in the cardiovascular area and very good poster sessions."

De la Pompa couldn't have begun to think about proposing Madrid as a Weinstein venue until events made it possible for these meetings to be held outside the US. This change was down to Antoon Moorman, a now-retired Dutch researcher who managed to bring this prestigious meeting to Holland. The 2014 Weinstein meeting thus breaks new ground in bringing the Weinstein Conference to Madrid, the first time in Europe the meeting will be held outside the

Netherlands. In steering Madrid's candidature, which beat off stiff competition from Shanghai, José Luis received encouragement from many colleagues, including CNIC scientists Miguel Torres and Miguel Manzanares and José María Pérez Pomares of the University of Malaga. For the Madrid meeting José Luis plans to introduce a shift in emphasis. "We want to include a focus on translational research, to try to show the relevance of research on cardiovascular development to cardiovascular health. This will mark a change from the classical conference format, which tends to be firmly centered on fundamental questions of development."



With the presentation of the candidature now behind him, de la Pompa is keen to acknowledge the help he received not only from colleagues but also from organizations such as the Madrid city authorities, the Spanish Developmental Biology Society, the Spanish networks for cell therapy (TerCel) and cardiovascular research (RIC). "The Madrid city authorities helped by supplying a video covering all that Madrid has to offer; we sent the Weinstein committee a document with information about the venue, the format for the meeting, possible funding sources and the video." Since then, almost four years ago, de la Pompa has himself participated in the selection of two venues for future Weinstein conferences, Boston and Durham (North Carolina).

Ahead now lies the anticipation of completing a project which the CNIC has, to coin a phrase, put its heart into. In May all the effort will be rewarded.



March 10, 2014
CNIC Seminar

"Transcriptional Control of Stem Cell Fate"

Brian Hendrich

Wellcome Trust-MRC Stem Cell Institute University of Cambridge UK



May 19, 2014
 CNIC Seminar

"Yeast genetics in mammalian stem cells"

Josef Penninger

Institute of Molecular Biotechnology (IMBA) Vienna Austria



March 24, 2014
CNIC Seminar

"Endothelial Dysfunction in Cardiovascular Disease"

Joseph Vita

Journal of the American Heart Association Boston USA



March 31, 2014
CNIC Seminar

"Caveolae:

Assembly and trafficking"

Ari Helenius

ETH Zürich, Institute of Biochemistry Switzerland



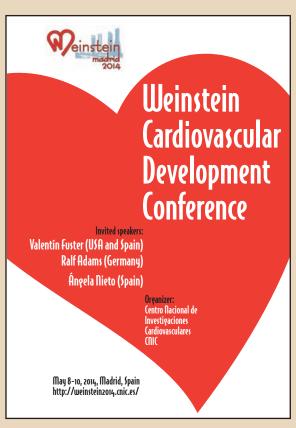
May 5, 2014

CNIC Seminar Gerd Heusch

Direktor des Institutes fuer Pathophysiologie, Universitaetsklinikum Essen Germany



WEINSTEIN CONFERENCE







For one day last year, the white coats did not form the only 'uniform' to be seen at the CNIC. On November 5, the Spanish national rugby team took over the center to present their new strip. The choice of venue was no coincidence, but rather the public celebration of an agreement signed in September

The most visible part of this agreement is the national team's new strip, and it was very fitting that they came to show it off at the home of the leading cardiovascular research center in Spain. The new shirt leaves no room for doubt about the commitment between these sporting and scientific bodies, and above all the shared commitment of both to promoting cardiovascular health.

Since November, when captain Pablo Feijóo led the team onto the field in a friendly against Japan, the shirt has included a new slogan, concise and simple, but with a big impact: *Unidos por el*

corazón (Hearts united). The first match with the new strip didn't go Spain's way, but all the spectators witnessed the FER's concern for cardiovascular health, something worth more than points scored.

ProCNIC Foundation president Luis de Carlos hit the mark in his speech presenting the new shirt, "It has always been said that rugby is a game played from the heart." And there could be no better proof of this than the new kit. Luis de Carlos also emphasized that the game teaches children "not only a sport, but also comradeship, loyalty, sacrifice and selflessness".

The so-called 'third half'—that period at the end of a match when departing players and spectators talk over the game—was a little different after the Spain–Japan fixture. There was less analysis than usual on tactics and strategy, and for once, but not once only, the heart was the star. As it should be.

CARDIO COMMITTED PATRON

FUNDACIÓN MAPFRE



The Pro-CNIC Foundation has moved on from a number traditionally linked to bad luck, but which in the CNIC's case has been associated with good fortune. In recent years the Pro-CNIC Foundation has been made up of thirteen businesses and organizations, but now an exciting development has increased this number to fourteen.

The change came in November last year, when Fundación Mapfre—the non profit organization set up by Spanish insurance giant MAPFRE—took on a new role as one of the patrons of the Pro-CNIC Foundation. This is the body that channels private investment to the CNIC, directed by the cardiologist Valentín Fuster, who also directs the Cardiovascular Institute at the Mount Sinai Hospital in New York.

The collaboration agreement was signed by Pro-CNIC Foundation president Luis de Carlos and MAPFRE president Antonio Huertas, in the presence of Dr. Fuster.

Fundación Mapfre joins the other thirteen companies and private organizations that support the largest cardiovascular research center in Europe and who share a commitment to cardiovascular research. Membership is about more than adding a logo to a website.
Fundación Mapfre injected €225,000 in 2013 and will add a further €400,000 in 2014 to support the Pro-CNIC Foundation, created in 2005.

More than just donors, the patrons in the Pro-CNIC Foundation contribute to decision making at the CNIC at the highest level, participating in its main managerial committees— the Governing Council and its Executive Committee. The Pro-CNIC Foundation uses a public-private finance model, still an infrequent occurrence in Spain. With this model, the aim is to guarantee the sustainability of the CNIC's scientific research projects.

According to Luis de Carlos, "it's great news that Fundación Mapfre is joining this group of businesses that, by sponsoring science, demonstrate a dual commitment: to promoting research and technological development as a sure sign of progress and increased competitiveness, and to achieving tangible improvements in the quality of life of all Spaniards."

At the CNIC, the relationship with the institutions that form the Pro-CNIC Foundation is valued very highly. As Dr. Fuster explains, "We have demonstrated that this is an effective and sustainable formula that, in short, guarantees excellence in cardiovascular research, which is the only way to advance in the fight against the main cause of death in developed countries, and that will soon also be the principal killer in poorer regions."

Antonio Huertas, for his part, is very pleased to be on board this project. "It's a privilege to participate in an initiative that shows such a commitment to research as the motor of development and to sponsorship of science. Fundación Mapfre and the CNIC share the desire to improve quality of life across society." He also stressed during the agreement ceremony that, since its creation, Fundación Mapfre had supported projects aimed at medical risk prevention and raising public awareness of healthy lifestyle habits, underlining that "the CNIC is a good example of these practices."

Before the new addition, the Pro-CNIC Foundation members were Acciona, BBVA, Endesa, Fundación Abertis, Fundación Mutua Madrileña, Fundación Botín, Fundación Ramón Areces, Fundación Repsol, Gas Natural Fenosa, Grupo Prisa, Inditex, la Caixa and Telefónica. These are now joined by the new family member, Fundación Mapfre. A warm welcome!